Formaldehyde Science – Response to 2011 NAS Recommendations

Epidemiology – Leukemia		
NAS Recommendation/ Conclusion	• Reliance on the peak-exposure metric [in the NCI cohort study) to determine causality in that study rather than the more conventional dose metric of cumulative exposure should be further justified, particularly in the absence of established modes of action. (page 83) • There is a noticeable lack of evidence of a causal relationship of formaldehyde exposure and Hodgkin lymphoma or leukemia. (page 100)	
New Publications	Neuss et al. 2010	"Exposure of human nasal epithelial cells to formaldehyde does not lead to DSNA damage in lymphocytes after co-cultivation" • Results of in vitro tests do not support a recently proposed hypothetic mechanism for formaldehyde induced leukemia by damaging circulating hematopoietic stem cells or hematopoietic progenitor cells in nasal passages, which then travel to the bone marrow and become initiated leukemic stem cells.
	Speit et al. 2010	"Occupational exposure to formaldehyde, hematotoxicity and leukemia-specific chromosome changes in cultured myeloid progenitor cells" — Letter to the Editor • Outlines the shortcomings of the Zhang 2010 study.
	Speit et al. 2011	"Does formaldehyde induce aneuploidy?" • Results confirm the clastogenicity of formaldehyde in cultured mammalian cells but exclude a significant aneugenic activity.
	Checkoway et al. 2012	"Critical review and synthesis of the epidemiologic evidence on formaldehyde exposure and risk of leukemia and other LHP malignancies" • At present, there is no consistent or strong epidemiologic evidence that formaldehyde is causally related to any of the LHM. • The absence of established toxicological mechanisms further weakens any arguments for causation.
In Press	Gentry et al	"Formaldehyde exposure and leukemia: reevaluation of the results from a study that is the regulatory focus for evidence of biological plausibility" • The assays used (CFU-GM) do not actually measure the proposed events in primitive cells involved in the development of AML • Evaluation of the available data indicates that the aneuploidy measured could not have arisen *in vivo*, but rather arose during *in vitro* culture
Pending Research	Coggan et al	Update of cohort of British formaldehyde workers

Epidemiology – Nasal Cancers		
NAS Recommendation/ Conclusion	• However, the fact that seven of nine NPC deaths occurred in the Wallingford, Connecticut, factory in the NCI cohort is intriguing. (page 100) • Given the importance of the NCI study to the formaldehyde assessment, EPA should make an effort to update its assessment once the NCI study findings on NPC become available. (page 64)	
New Publications	Speit et al. 2011	"Analysis of micronuclei, histopathological changes and cell proliferation in nasal epithelium cells of rats after exposure to formaldehyde by inhalation" • Study demonstrates local cytotoxic effects in the nose of rats after inhalation of formaldehyde; • Induction of micronuclei in the nasal epithelium as an indicator of a mutagenic effect was not seen.
	Zeller J. et al. 2011	"Assessment of genotoxic effects and changes in gene expression in humans exposed to formaldehyde by inhalation under controlled conditions" • Human inhalation study did not lead to genotoxic effects in peripheral blood cells and nasal mucosa • No effect on the expression of the FDH gene • Did not cause alterations in the expression of genes in a microarray analysis with nasal biopsies and peripheral blood cells.
	Zeller J et al. 2011	"Is individual nasal sensitivity related to cellular metabolism of formaldehyde and susceptibility towards formaldehyde-induced genotoxicity?" • In this human study, there was no close correlation between the various indicators of cellular sensitivity towards formaldehyde induces genotoxic effects and no subgroups were identified with particular mutagen sensitivity towards formaldehyde.
In Press	Beane-Freeman et al.	"Mortality from solid tumors among workers in formaldehyde workers: an update of the NCI cohort" • Analysis includes 1,006 deaths that occurred from 1980 to 1994, but were not identified in previous analyses of the cohort • 10 additional years of follow-up and deaths (1994-2004)from previous published reports

Mode of Action/Biological Plausibility		
NAS Recommendation/ Conclusion	• The committee concludes that the issue of whether inhaled formaldehyde can reach the systemic circulation is extremely important in assessing any risk of adverse outcomes at nonrespiratory sites associated with inhalation of formaldehyde (page 27) • The mode of action for formaldehyde-induced Hodgkin lymphoma and leukemia has not been clearly established. Moreover, the highly limited systemic delivery of formaldehyde draws into question the biologic feasibility of causality between formaldehyde exposure and the two cancers. Thus, substantial uncertainties in using Hodgkin lymphoma and leukemia for consensus cancer risk estimation remain. (page 107)	
New Publications	Lu et al. 2010	"Distribution of DNA adducts caused by inhaled formaldehyde is consistent with induction of nasal carcinoma but not leukemia" • Methodology can distinguish between endogenous and exogenous (inhaled) formaldehyde • Exogenous FA adducts and crosslinks were found in rate respiratory nasal mucosa, but did not form in sites remote to the point of entry • Strong evidence for a genotoxic and cytotoxic MOA for carcinogenesis in nasal
	Neuss et al. 2010	"Inhalation of formaldehyde does not induce genotoxic effects in broncho-alveolar lavage (BAL) cells of rats" • Animal inhalation study results question the biological significance of previously reported genotoxic effects in the lung of rats after formaldehyde inhalation.
	Just et al. 2011	"Genetic polymorphisms in the formaldehyde dehydrogenase gene and their biological significance" • Study did not identify biologically relevant polymorphisms in transcribed regions of the FDH gene, which may lead to inter-individual differences in the metabolic inactivation of formaldehyde.
	Lu et al. 2011	"Molecular dosimetry of N^2-hydroxymethyl-dG DNA adduct in rats exposed to formaldehyde" • Demonstrated that formaldehyde induces exogenous DNA adducts in a highly nonlinear fashion. • Examination of the ratio of exogenous versus endogenous formaldehyde DNA adducts clearly demonstrates that endogenous DNA adducts predominate at low ppm doses and that ppb exposures contribute miniscule amounts of exogenous DNA adducts. • The data generated in this study provide new scientific evidence for the assessment of risk resulting from formaldehyde exposure through inhalation.

Mode of Action/Biological Plausibility (continued)		
New Publications	Moeller et al. 2011	"Determination on N^2-hydroxymethyl-dG adducts in nasal epithelium and bone marrow of non-human primates following $^{13}CD_2$-formaldehyde inhalation exposure" • The presence of endogenous and exogenous *N2*-hydroxymethyl-dG adducts in DNA from nasal mucosa and bone marrow of cynomolgus macaques exposed to 1.9 and 6.1 ppm of [13CD2]-formaldehyde for 6 hours a day for 2 consecutive days was investigated. • Both exogenous and endogenous adducts were readily detected and quantified in the nasal tissues of both exposure groups, with an exposure dependent increase in exogenous adducts observed. • In contrast, only endogenous adducts were detectable in the bone marrow, even though ~10 times more DNA was analyzed.
	Swenberg et al. 2011	"Endogenous versus exogenous DNA adducts: their role in carcinogenesis, epidemiology, and risk assessment" • The fact that formaldehyde is present in every living cell cannot be ignored when conducting a cancer risk assessment for inhaled formaldehyde. • Now that the relationship between the number of exogenous DNA adducts derived from the inhaled formaldehyde exposure and the number of endogenous adducts present in bone marrow is known, we have to seriously question the biological plausibility that inhaled formaldehyde causes LEU and HL, and start asking much more probing questions about the epidemiology data. • Less than one exogenous DNA adduct was present for every 13,900 endogenous formaldehyde adducts. It is difficult to conceive of a mechanism by which 1/13,900 identical DNA adducts could drive the biology that leads to carcinogenesis.
	Kuehner et al. 2012.	"Analysis of leukemia-specific aneuploidies in cultured myeloid progenitor cells in the absence and presence of formaldehyde exposure" • Our results do not support the assumption of a specific effect of FA on myeloid progenitor cells as a potential mechanism for the induction of leukemia.
	Swenberg et al. 2012	"Formaldehyde carcinogenicity research: 30 years and counting for mode of action, epidemiology, and cancer risk assessment" • Our knowledge regarding the MOA of FA-induced carcinogenesis is much greater • Most of this knowledge has not been applied in recent assessments of formaldehyde risk

Mode of Action/Biological Plausibility (continued)		
New Publications	Zeller et al. 2012	"Investigation of potential susceptibility to formaldehyde genotoxicity" • None of the study groups showed particular mutagen sensitivity toward FA-induced genotoxicity. • These results suggest that a low scaling factor to address possible human inter-individual differences in FA-induced genotoxicity could be reasonable.
	Kleinnijenhuis et al. 2013	"The determination of exogenous formaldehyde in blood of rats during and after inhalation exposure" • Animal inhalation study concluded that the inhalation of 13C–FA at 10ppm for 6h did not result in an increase of the total FA concentration in blood.
In Press	Swenberg et al.	"Characterization of endogenous versus exogenous DNA adducts following inhalation exposure to formaldehyde in rats and non-human primates"
Pending Research	Swenberg et al.	28-day rodent study – determination of steady state concentrations of DNA adducts
Use of Predictive Models and Other Approaches		
NAS Recommendation/ Conclusion	• EPA is encouraged to consider the use of alternative extrapolation models for the analysis of the cancer data; this is especially important given the use of a single study, the inconsistencies in the exposure measures, and the uncertainties associated with the selected cancers. (page 10) • The committee recommends that EPA provide alternative calculations that factor in nonlinearities associated with the cytotoxicity compensatory cell proliferation mode of action and assess the strengths and weaknesses of each approach.(page 44) • The committee recommends that for completeness and transparency the BBDR models published by Conolly et al. (2003, 2004), with the flaw in one numeric approach identified by EPA corrected, be used in the draft IRIS assessment and that the results be compared with those of the approach that was used in the draft assessment. (page 44)	
In Press	Schroeter et al.	"Nasal dosimetry prediction of inhaled formaldehyde incorporating endogenous formaldehyde levels"
	Starr & Swenberg	"A novel bottom-up approach to carcinogenic risk assessment for endogenous chemicals" • Simple linear approach that capitalizes on new molecular dosimetry to estimate upper bound NPC and leukemia risks. • Extrapolation upward from background (endogenous) exposures and background risks • Comparison shows EPA risk estimates from epidemiologic data to be disturbingly high

Endogenous Formaldehyde		
NAS Recommendation/ Conclusion	• The committee emphasizes that the natural presence of various concentrations of formaldehyde in target tissues remains an important uncertainty with regard to assessment of the additional dose received by inhalation. (page 23)	
New Publications	Reiss et al. 2010	"Experimental setup and analytical methods for the non-invasive determination of volatile organic compounds, formaldehyde and NOx in exhaled human breath" • Due to rapid conversion of formaldehyde with a half-life of about 1 minute in blood and the large Henry constant . . . high levels of formaldehyde cannot be expected in exhaled breath. • Concentrations in the lower ppb range seem to be realistic in dependence of nutrition and health status.
	Salthammer et al. 2011	Formaldehyde in the indoor environment • Formaldehyde in breath = 1.2-72.7 ppb; median = 4.3 ppb (deep lung portion)

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